REMARKS

Claims 50-52 have been cancelled and claims 45 and 70 have been amended without prejudice.[9] Support for the amended claims can be found throughout the application as originally filed. Attached hereto is a marked-up version of the changes made to the claims by this Amendment. The attachment is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**"

I. The Written Description Rejection

Claims 45-110 stand rejected under 35 U.S.C. § 112, ¶ 1, as allegedly lacking sufficient written description. The Examiner argues that the specification fails to provide sufficient relevant identifying characteristics that identify members of the genus of antibodies that bind gp55, gp95, gp115 or gp210 antigens.

Applicant respectfully traverses to the extent the rejection may be held to apply to the amended claims. In particular, the Examiner objects to the identification of the glycoproteins gp55, gp95, gp115 or gp210 absent a "structure, formula, chemical name or physical properties." However, *Fiers v. Sugano* recognizes that a chemical material is properly claimed by means of a process and that conception can occur (and thus the written description requirement can be satisfied) when one is able to describe the chemical material by its method of preparation. *See Fiers v. Sugano*, 25 U.S.P.Q.2d 1601, 1604-1605 (Fed. Cir. 1993) ("in addition to being claimable by structure or physical properties, a chemical material can be claimed by means of a process."). The chemical identity of the recited binding site (and the corresponding antigenic site) is clearly described by the process of isolation.

For instance, Example 2 and the references cited therein amply describe the method of preparing these representative antibodies and one skilled in the art would recognize how to isolate these antibodies from the methods disclosed in the specification. One skilled in the art would instantly recognize that the recited glycoproteins were isolated from rats immunized with selected myelomas (as described by the reference cited therein), from which hybridomas were produced via methods well know in the art, and that Ig-producing hybridomas were selected by routine immunofluorescent staining. One skilled in the art would further recognize selection of the recited antibodies via standard flow cytometry analysis and immunoprecipitation.

Further, the "gp" nomenclature is merely a convenience only and not an intended limitation of the claim. Methods of isolating an antibody and corresponding antigen, are well known in the art and are sufficiently disclosed in the specification (see, e.g., pg. 24-25, and the references cited therein). The "gp" nomenclature is used merely as a convenience to quickly and easily identify the antibodies selected by the recited method without reciting the method in its entirety every time when referring to the selected antibodies.

Moreover, in contrast to the Examiner's contention that the specification merely cites a "potential" method of isolating a protein, Example 2 in the specification explicitly details repeatable experimental conditions under which the representative antibodies may be identified and isolated (see e.g., pg. 24-25, and the references cited therein). Thus, the written description requirement is satisfied by disclosing the isolation of antibody and its corresponding antigen by the method of preparation. One skilled in the art would understand that Applicant was in possession of the method of preparing a binding site (antibody) corresponding to an antigen on the surface of a target diseased cell, and would have no difficulty in making and using functional antigens and antibodies that fall within the scope of the claims. As a result, the rejection is

traversed and Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

II. The Enablement Rejection

Claims 45-110 stand rejected under 35 U.S.C. § 112, ¶ 1, as allegedly not being enabled. The Examiner indicates that the specification has not enabled the breadth of the claimed invention in that the claims allegedly encompass an antibody with a specificity against any cell surface protein on any target cell recited in the claims, and posits that the state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and/or used. Respectfully, this rejection is traversed as set forth below.

Specifically, the Examiner objects "because the claims encompass a composition which comprises an antibody with a specificity against any cell surface protein on any of the said target cells recited in the instant claims." First, Applicant has provided amended claims 45 and 70, neither of which recite an antibody with a specificity against any cell surface protein. Second, the specification does not teach that the recited binding sites (antibodies) are specific against *any* cell surface protein. Instead, the specification teaches that the antigens located on the surface of target cells need not be unique to those target cells (see e.g., pg. 7, 22-23) or the binding sites. Because the bridging molecules in some embodiments of the invention are attached to the tumor or target diseased cells *in vitro* prior to treating a patient *in vivo*, the need for unique specificity is eliminated. Therefore, the specification does not teach an antibody specific to any and all cell surface proteins, as claimed by the Examiner.

The Examiner further argues that the state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and/or used.

Applicant submits that the specification enables one skilled in the art to make and/or use the invention. As explained above, Applicant believes sufficient disclosure exists in the specification enabling one skilled in the art to isolate an appropriate binding site, for example, associated with antigens located on the surface of target diseased cells (see, e.g., pg. 24-25). One skilled in the art can make and use the antibodies and corresponding antigens made by the recited method without undue experimentation.

The Examiner also alleges that the specification does not specify the bispecific monoclonal antibodies (mAb) used in Example 16, a repeatable method of obtaining them or bispecific monoclonal antibodies that are readily available to the public.

The specification discloses the exact bispecific mAb anti-CD28 as well as a repeatable method for obtaining the bispecific mAb on pages 50-51. Also note that the anti-CD28 nomenclature is explained in further detail, e.g., on page 25. The methods for assembling and isolating these Bi-MAbs are described throughout the specification (see e.g., pg. 25, lines 1-17).

Further, resources for obtaining bispecific monoclonal antibodies readily available to the public are disclosed on page 7 (citing U.S. Patent Nos. 5,637,481, 5,635,602, 5,635,600, 5,591,828, 5,292,668, 5,582,996).

The Examiner further alleges that the specification does not disclose monoclonal antibodies against a 55, 95, 115, or 210 kDa glycoprotein, a repeatable method of obtaining them or monospecific antibodies that are readily available to the public.

With respect to antibodies specific to 55, 95, 115, or 210 kDa glycoprotein, Applicant submits that, as noted above, the methods of isolating binding sites (antibodies) specific to a diseased target cell are amply described in the specification (e.g., pg. 24-25, and references incorporated therein). The "gp" nomenclature is purely for convenience only and is not intended

as a structural limitation. One skilled in the art would have no difficulty making or using the invention by isolating antibodies as disclosed in the specification.

In view of the above, Applicant respectfully submits that the rejection has been overcome. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

III. The Provisional Double Patenting Rejections

Claims 45-110, stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly being unpatentable over claims 103-139, of co-pending application no. 08/872,527.

Applicant respectfully requests that the Examiner hold this matter in abeyance until the claims in the application are to be found otherwise allowable, as any further response at this time would be premature in view of the fact that the claims in this or the other application could be amended prior to issuance.

IV. The Indefiniteness Rejection

Claims 45-110 stand rejected under 35 U.S.C. § 112, ¶ 2, as allegedly being indefinite. In particular, the recitation of "substantially free" in claim 70 is allegedly indefinite because the metes and bounds of the said phrase are unclear. The Examiner further objects to the recitation of "gp55", "gp95", "gp115" or "gp210" as indefinite because the characteristics of the said "gp55", "gp95", "gp115" or "gp210" antigens and hence, that of the said antibodies, are not known.

With respect to claim 70, the term "substantially free" would be understood by one or ordinary skill in the art. Further, as noted above, the use of "gp55", "gp95", "gp115" or "gp210" nomenclature is merely for convenience only and the recited binding sites are clearly supported by the specification. Example 2 explicitly discloses standard methods of their preparation, which are well known in the art. One skilled in the art would have no difficulty understanding the subject matter of the amended claims. In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

CONCLUSION

Applicant believes that this Response will now place the application in condition for allowance. If the amount enclosed is incorrect, please charge or credit Baker & McKenzie Deposit Account No. 50-1881 in the appropriate amount. Should any issues remain unresolved, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 45 and 70 were amended without prejudice.

--45. A method of preparing a pharmaceutical composition or therapeutic vaccine, said method comprising the steps of:

(a) providing a plurality of hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells;

(b) treating said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells to increase the levels of [CD28, 4-1BB, or CTLA-4] primary or costimulatory molecules in said cells;

(c) providing a plurality of a bispecific monoclonal antibodies, each of said antibodies comprising a binding site for a CD28, 4-1BB or CTLA-4 molecule on the surface of T cells in a patient mammal and a binding site for a gp55, gp95, gp115 or gp210 antigen;

(d) attaching said bispecific monoclonal antibodies to said cells; and

(e) thereafter collecting a pharmaceutically effective amount of said cells with said bispecific monoclonal antibodies attached thereto; wherein said steps (c) and (d) are performed either before or after said step (b).

70. An immunogenic composition, comprising:

a pharmaceutically effective amount of one or more isolated autologous hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells which express one or more [CD28, 4-1BB, or CTLA-4] primary or costimulatory molecules at a level higher than in said cells in a patient mammal; and

a pharmaceutically effective amount of one or more bispecific monoclonal antibodies comprising a binding site for a CD28, 4-1BB or CTLA-4 molecule on the surface of T cells in a

patient mammal, and a binding site for a gp55, gp95, gp115, or gp210 antigen, wherein said bispecific monoclonal antibodies are attached to said cells, and wherein said composition is substantially free of bispecific monoclonal antibodies not attached to said cells.